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(54) **Adduct of topiramate and tramadol hydrochloride and uses thereof**

(57) This invention relates to a new pharmaceutically useful compound which is a stoichiometrically 1:1 adduct of tramadol hydrochloride and topiramate, to the manufacture and use thereof.

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**Description****Brief description of the invention**

- 5 [0001] This invention relates to a new pharmaceutically useful compound which is a stoichiometrically 1:1 adduct of tramadol hydrochloride and topiramate, to the manufacture and use thereof.

**Background of the Invention**

- 10 [0002] A number of effective anticonvulsants including the compound 2,3:4,5-bis-O-(1-methylethylidene)- $\beta$ -D-fructopyranose sulfamate, also known as topiramate, have been disclosed in U.S. Pat. No. 4,513,006. Topiramate is useful in the treatment of human epilepsy in that it is effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. Faught et. al., *Epilepsia* 36 (S4) 33, 1995; S. K. Sachdeo, et al., *Epilepsia* 36 (S4) 33, 1995). Topiramate is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures.

- 15 [0003] Recent preclinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate is effective in treating some other disorders. One of these is neuropathic pain. Neuropathic pain remains one of the "frontiers" of pain management. There is a significant unmet need for efficacious and tolerable pharmacotherapy, making neuropathic pain an area of intense research interest. The term "neuropathic pain" is applied to any acute or chronic pain syndrome in which the sustaining mechanism for the pain is believed to involve abnormal transmission (peripheral) or processing (central) of somatosensory input.

U.S. Pat. No. 5,760,007 discloses topiramate as useful for the treatment of neuropathic pain.

- 20 [0004] A class of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkylring, are disclosed in U.S. Pat. No. 3,652,589. Among these is the compound (1R,2R or 1S,2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol commonly known as tramadol, which is specifically disclosed therein. Tramadol typically is used as the hydrochloride salt form.

- 25 [0005] A series of articles pertaining to the pharmacology, toxicology and clinical studies of tramadol hydrochloride are found in *Arzneim. Forsch.*, (Drug Res.), 1978, 28(1), 114. The Abstracts of the VI th World Congress on Pain, April 1-6 (1990), disclose that tramadol hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that tramadol hydrochloride lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., *Arzneim. Forsch.*, (Drug Res.), 1978, 28(1), 183), constipation (I. Arend et al., *Arzneim. Forsch.*, (Drug Res.), 1978, 28(1), 199), tolerance (L. Flohe et al., *Arzneim. Forsch.*, (Drug Res.), 1978, 28(1), 213) and abuse liability (T. Yanagita, *Arzneim. Forsch.*, (Drug Res.), 1978, 28(1), 158). Tramadol hydrochloride's 'atypical' combination of non-opioid and opioid activity makes tramadol a very unique drug. Tramadol hydrochloride is currently marketed as an analgesic.

- 30 [0006] Opioids have for many years been used as analgesics to treat severe pain. They, however, produce undesirable side effects and, as a result, cannot always be given repeatedly or at high doses. The side effect problems are well documented in the literature. See, for example, T. Reisine and G. Pasternak in "Goodman and Gilman's, The Pharmacological Basis of Therapeutics", 9th edition; Hardman et al.; McGraw-Hill, New York, 1996; Chapter 23; pages 521 - 555 wherein it is disclosed that morphine and its congeners, e.g., codeine, hydrocodone and oxycodone are opioid agonist analgesics that exhibit side effects such as respiratory depression, constipation, tolerance and abuse liability.

- 35 [0007] To reduce the side effect problems of opioids, opioids have been combined with other drugs, including non-opioid analgesic agents, which lower the amount of opioid needed to produce an equivalent degree of analgesia. It has been claimed that some of these combination products also have the advantage of requiring less of each ingredient while producing a synergistic analgesic effect.

- 40 [0008] As an analgesic, tramadol hydrochloride has been combined with both opioid and non-opioid analgesic drugs. Such compositions have exhibited synergistic effects in treating pain while using less of each ingredient to produce an equivalent degree of analgesia. Specifically, U.S. Pat. No. 5,516,803 discloses the composition of tramadol hydrochloride and a NSAID, particularly ibuprofen. U.S. Pat. No. 5,468,744 discloses tramadol hydrochloride plus any of oxycodone, codeine or hydrocodone and U.S. Pat. No. 5,336,691 discloses tramadol hydrochloride in combination with acetaminophen.

- 45 [0009] WO-01/13904 relates to a pharmaceutical composition comprising a combination of a tramadol material and an anticonvulsant drug and to the pharmacological use of the composition in treating conditions of pain and neurologic or psychiatric disorders. The composition produces a combination product having improved properties, requiring less of each ingredient and producing a synergistic effect.

- 50 [0010] WO-01/13904 further discloses that in animal studies using the Chung model of post-nerve constriction injury, both tramadol hydrochloride and topiramate are significantly active and reach 100% MPE (Maximum Possible Effect)

as the dose is escalated. When topiramate and tramadol hydrochloride are co-administered in this model the ED<sub>50</sub> of both drugs is dramatically reduced, suggesting synergy of analgesic effect. The degree of synergy varies across ratios in this model with those ratios in which tramadol hydrochloride predominates displaying the greatest synergy.

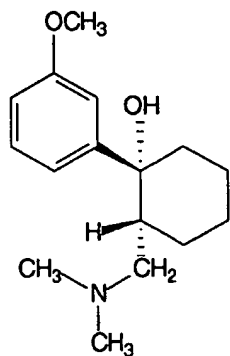
[0011] Compositions including combinations of topiramate and tramadol hydrochloride have been found to be relatively unstable, in particular due to the instability of topiramate.

[0012] Moreover, the half lives of topiramate and tramadol are largely different in that tramadol's half life is relatively short while that of topiramate is relatively longer. Plasma levels of tramadol therefore will sink more rapidly below effectivity thresholds than those of topiramate, which is undesirable because there is a need to keep the bloodplasma levels of both active ingredients at a sufficient level, in particular if the above mentioned synergistic effect is desired. Therefore there is a need to provide pharmaceutical compositions that release both topiramate and tramadol in effective quantities during a sufficiently long period of time.

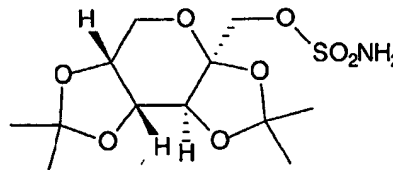
[0013] Furthermore, it is an object of the present invention to produce a combination product with tramadol hydrochloride and topiramate having improved properties. It is also an object of the present invention to produce a combination product with tramadol and topiramate wherein the combination has a synergistic effect while being stable and providing a constant and sustained release of both active ingredients. A further object of the present invention is to provide a method for treating conditions of pain, in particular neuropathic pain, and neurological or psychiatric disorders in mammals.

#### Summary of the invention

[0014] This invention relates to a chemical compound which is an adduct of tramadol hydrochloride and topiramate. This adduct can be represented by the following chemical structure:



HCl



(I)

1R, 2R-tramadol hydrochloride

Topiramate

[0015] The adduct in particular is the 1:1 adduct.

[0016] In particular, the tramadol hydrochloride in the adduct is one enantiomeric form, namely (1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexan-1-ol hydrochloride or 1R,2R-tramadol hydrochloride.

[0017] In another aspect the invention concerns a process for manufacturing the 1:1 adduct of tramadol hydrochloride and topiramate of formula (I) comprising crystallizing the 1:1 adduct from a suitable solvent or by storing a dry powder mixture of topiramate and tramadol hydrochloride under high relative humidity at elevated temperatures.

[0018] In still another aspect, the invention provides a process for preparing enantiomerically pure tramadol hydrochloride. The (1S,2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexan-1-ol hydrochloride enantiomer, i.e. 1S,2S-tramadol hydrochloride, remains in the mother liquor when crystallizing the 1:1 adduct. The (1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexan-1-ol hydrochloride enantiomer, i.e. 1R,2R-tramadol can be isolated of formula(I) by separating the 1R, 2R tramadol hydrochloride from the topiramate in the adduct.

[0019] In a further embodiment, the invention relates to pharmaceutical compositions comprising an effective amount of a 1:1 adduct of tramadol hydrochloride and topiramate. The invention also provides a process for preparing said pharmaceutical formulations comprising mixing the adduct with appropriate carrier materials.

[0020] Furthermore, the invention concerns a method of treating a warm blooded animal suffering from neuropathic pain, said method comprising the administration of an effective amount of the 1:1 adduct of tramadol hydrochloride and topiramate described herein.

## 5 Detailed description of the invention

[0021] Tramadol is the compound (1R,2R or 1S,2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexan-1-ol. Preferably tramadol is used as a salt form, in particular its hydrochloride salt. Tramadol hydrochloride is commercially available from Grunenthal or may be made by the process described in U. S. Patent No. 3,652,589.

10 [0022] Topiramate is the compound 2,3:4,5-bis-O-(1-methylethylidene)- $\beta$ -D-fructopyranose sulfamate and can be prepared according to processes described in U.S. Pat. No. 4,513,006.

[0023] The adduct of formula (I) can be manufactured in its pure form by dissolving topiramate and tramadol hydrochloride at a suitable molar ratio in a suitable solvent e.g. a lower alkanol, in particular a C<sub>1-3</sub> alkanol such as methanol, ethanol or 1- or 2-propanol, at elevated temperature. In an embodiment of this method of manufacture, the two starting materials are dissolved in the solvent at elevated temperature, or the starting materials can be introduced in the solvent which is brought to an elevated temperature, e.g. at a temperature above 30°C, or above 40°C. In one embodiment this temperature is about 40°C. The whole is allowed to cool to temperatures below room temperature, e.g. to a temperature below 10°C, or to a temperature that is in the range of 2-8 °C, or below 0 °C, for example even as low as -18°C. Cooling may be done immediately or gradually, over a certain period of time, or stepwise. The adduct crystallizes and the crystals may then be isolated from the mother liquor, e.g. by filtration.

20 [0024] The molar ratios of topiramate : tramadol hydrochloride used in this procedure may vary. For example molar ratios of topiramate : tramadol hydrochloride in the range of 1 : 1 and 1 : 4 can be used. Preferred are molar ratios that approximate 1 : 2, in one embodiment said ratio is about 1 : 2.

[0025] The resulting adduct is a crystalline compound that can be characterized by its melting point, X-ray diffraction or by spectroscopic methods such as IR.

25 [0026] Single crystal X-ray diffractometric results showed that the crystalline adduct consists of topiramate molecular moieties and tramadol molecular moieties in a 1:1 ratio alternating in a crystal lattice with Cl<sup>-</sup> ions arranged in between these two molecular moieties. The single crystal X-ray diffractometric structural analysis did not allow the determination of the exact position of any of the hydrogen atoms and consequently the position of the proton derived from the hydrogen chloride entity could not be determined. Without being bound to theory it is assumed that, given the basicity of tramadol, the hydrochloride proton is most likely coordinated to the nitrogen atom of tramadol, thus forming a tramadol -H<sup>+</sup> ionic moiety.

[0027] The new adduct of formula (I) is stable and shows enhanced bioavailability. In particular, topiramate has prolonged stability in this adduct.

35 [0028] An additional feature of the present invention comprises the fact that it allows the preparation of (1S,2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexan-1-ol hydrochloride, herein referred to as 1S,2S-tramadol hydrochloride, or enantiomerically enriched mixtures of 1S,2S-tramadol hydrochloride. Said enantiomerically enriched mixtures are mixtures of 1R,2R-tramadol hydrochloride and 1S,2S-tramadol hydrochloride in which the latter is predominantly present. In one embodiment said enantiomerically enriched mixtures contain at least about 80 % (w/w, calculated relative to the total amount of tramadol hydrochloride) of 1S,2S-tramadol hydrochloride, or at least 90 %, or at least 95 % or even at least 98 % of 1S,2S-tramadol hydrochloride.

40 [0029] In a similar feature of the present invention comprises the fact that it allows the preparation of (1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexan-1-ol hydrochloride, herein referred to as 1R,2R-tramadol hydrochloride, or enantiomerically enriched mixtures of 1R,2R-tramadol hydrochloride. Said enantiomerically enriched mixtures are mixtures of 1S,2S-tramadol hydrochloride and 1R,2R-tramadol hydrochloride in which the latter is predominantly present. In one embodiment said enantiomerically enriched mixtures contain at least about 80 % (w/w, calculated relative to the total amount of tramadol hydrochloride) of 1R,2R-tramadol hydrochloride, or at least 90 %, or at least 95 %, or even at least 98 % of 1R,2R-tramadol hydrochloride.

45 [0030] These products can be isolated from the reaction products of the above described procedures to prepare the adduct of formula (I).

50 [0031] The 1S,2S-tramadol HCl isomer, or enantiomerically enriched mixtures thereof, can be obtained from the mother liquor when preparing the 1:1 adduct of formula (I) following the crystallization procedure described above. The crystals are filtered off and the 1S,2S-tramadol HCl is isolated by preparative chromatography or selective crystallization. If deemed necessary, prior to this isolation step, a second crystallization step may be introduced, i.e. the mother liquor is brought again to elevated temperature, optionally with the addition of additional topiramate, whereupon the whole is cooled again as described above to allow a second batch of adduct of formula (I) to crystallize.

55 [0032] The 1R,2R-tramadol hydrochloride isomer, or enantiomerically enriched mixtures thereof, can be obtained from the adduct of formula (I) by separating the 1R,2R-tramadol from the topiramate in the adduct.

[0033] In the latter instance, the adduct is split into its components topiramate and 1R,2R-tramadol hydrochloride. This can be accomplished by dissolving the adduct in a suitable solvent, such as a halogenated hydrocarbon, e.g. dichloromethane, chloroform and the like. The two components can be separated e.g. by preparative chromatography or by a recrystallization procedure. Alternatively, the adduct of formula (I) can be contacted with a solvent in which topiramate is not very soluble, but tramadol HCl is, e.g. a polar solvent such as water.

[0034] This can be done, for example, by stirring up a mixture of the adduct of formula (I), which has been made into small particles, in water, optionally while slightly heating. The topiramate is separated off, e.g. by filtration. The filtrate contains the desired 1R,2R-tramadol hydrochloride.

[0035] Or the adduct of formula (I) can be subjected to an appropriate extraction procedure. In this instance, the extract contains the desired 1R,2R-tramadol hydrochloride.

[0036] The solutions containing 1R,2R-tramadol hydrochloride can be allowed to crystallize for example by evaporating a sufficient amount of water and allowing the product to crystallize upon cooling.

[0037] This procedure allows the preparation of enantiomerically pure 1R,2R-tramadol hydrochloride.

[0038] 1S,2S-tramadol or 1R,2R-tramadol can be used as an active ingredient in pharmaceutical formulations which can be applied for the same indications as (1R,2R; 1S,2S)-tramadol. Preferably 1S,2S-tramadol or 1R,2R-tramadol is used in its acid-addition salt form, more preferably as a hydrohalide salt form, in particular as the hydrochloride salt form. These formulations can be prepared following the same or similar procedures as described hereinafter.

[0039] The adduct of formula (I) can be used as an active ingredient in pharmaceutical formulations. To prepare such formulations, an effective amount of the said adduct is mixed with one or more suitable carriers according to conventional pharmaceutical compounding techniques. Preferred are solid formulations for oral application form such as, for example, powders, capsules and tablets. In the case of oral solid preparations, carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, may be used. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The pharmaceutical compositions of the present invention will generally be in the form of a dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, wherein the preferred amount of each of the active ingredient to be contained therein is determined by the aforementioned ratios.

[0040] Dosage forms prepared from the adduct of formula (I) will evidently contain tramadol hydrochloride: topiramate in a 1:1 w/w ratio. In a number of instances it may be desirable to prepare formulations in which this ratio is other than 1:1. These can be prepared by adding appropriate amounts of additional tramadol hydrochloride or topiramate to the mixture.

[0041] The pharmaceutical compositions of the present invention are useful for treating conditions of pain and certain neurological and psychiatric disorders in mammals by the administration of a composition comprising the tramadol hydrochloride/topiramate adduct of formula (I) as defined herein. Those skilled in the art of treating mammalian pain know that the types of pain experienced by mammals are varied.

[0042] Examples of conditions of mammalian pain include, but are not limited to, centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, progressive disease related pain and neuropathic pain states, all of which would include acute pain such as caused by acute injury, trauma or surgery; chronic pain such as caused by neuropathic conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes or cluster or migraine headaches; and inflammatory condition pain such as caused by osteoarthritis, rheumatoid arthritis or as sequela to disease, acute injury or trauma. The composition of the present invention is also useful in the treatment of certain neurological and psychiatric disorders including, but not limited to, bipolar disorder, psychosis, post-traumatic stress disorder, social phobia, obsessive-compulsive disorder; movement disorders such as akathisia, restless leg syndrome, tardive dyskinesia or central tremor; neurodegeneration in diseases such as ischemic (acute, delayed, recovery) or degeneration of nervous system cells due to Alzheimer's disease, Parkinson's disease or surgery; particularly, open-chest surgery; and, more particularly, open-heart or bypass surgery.

#### Example

[0043] Two moles of tramadol hydrochloride and one mole of topiramate were mixed in ethanol and the whole is heated to 40 ° C for sufficient time to allow the solid drug substances to dissolve. Subsequently the mixture is cooled to a temperature of about 2 - 8 ° C whereupon crystals start forming. The whole is allowed to stand for several hours at that temperature allowing the formation of the remainder of the crystals. The whole is filtrated while cool and the crystals are dried. The resulting 1:1 adduct had a melting point of about 161° C (onset temperature).

Claims

1. 1:1 adduct of topiramate and tramadol hydrochloride.
2. The adduct of claim 1 having a melting point of about 161° C (onset temperature).
3. A process for preparing the adduct as claimed in claims 1 or 2 **characterized in that** topiramate and tramadol hydrochloride are dissolved in an appropriate solvent which is brought to elevated temperatures and then cooled to a temperature which is below room temperature and letting the adduct crystallize.
4. A process according to claim 3 wherein the appropriate solvent is ethanol and the crystals are separated from the mother liquor by filtration.
5. A pharmaceutical composition comprising a suitable carrier and an effective amount of the adduct claimed in claims 1 or 2.
6. A process for preparing a composition as claimed in claim 4 **characterized in that** the adduct is intimately mixed with the carrier.
7. A method of treating a warm blooded animal suffering from neuropathic pain, said method comprising the administration of an effective amount of the 1:1 adduct of tramadol and topiramate hydrochloride claimed in claims 1 or 2.
8. A process for preparing 1S,2S-tramadol hydrochloride, or enantiomerically enriched mixtures of 1S,2S-tramadol hydrochloride, **characterized in that**
  - (a) topiramate and tramadol hydrochloride are dissolved in an appropriate solvent which is brought to elevated temperatures and then cooled to a temperature which is below room temperature and letting the adduct crystallize
  - (b) the crystals are separated from the mother liquor by filtration
  - (c) separating the 1S,2S-tramadol hydrochloride from the mother liquor.
9. A process according to claim 8 wherein the 1S,2S-tramadol hydrochloride is isolated by preparative chromatography or selective crystallization.
10. A process for preparing 1R,2R-tramadol hydrochloride, or enantiomerically enriched mixtures of 1R,2R-tramadol hydrochloride, **characterized in that**
  - (a) the adduct as claimed in claims 1 or 2 is split into its components topiramate and 1R,2R-tramadol hydrochloride by dissolving the adduct in a suitable solvent, and the two components are separated by an appropriate separation method; or
  - (b) the adduct as claimed in claims 1 or 2 is contacted with a solvent in which topiramate is not very soluble, but tramadol hydrochloride is.



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# PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 02 07 7019

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D, X	WO 01 13904 A (ORTHO MCNEIL PHARM INC) 1 March 2001 (2001-03-01) * table 1 * * claims 1,5,12,13 * * page 16, line 1-5 *	1,5-7	A61K31/35 A61P25/04 //(A61K31/35, 31:135)
A	DE 199 27 689 A (GRUENENTHAL GMBH) 21 December 2000 (2000-12-21) * the whole document *	1-10	
A	DE 199 40 740 A (GRUENENTHAL GMBH) 1 March 2001 (2001-03-01) * abstract *	1-10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			A61K
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>Although claim 7 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.</p>			
Place of search		Date of completion of the search	Examiner
MUNICH		9 October 2002	Veronese, A
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>&amp; : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03.82 (P04C07)

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 02 07 7019

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on  
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09-10-2002

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0113904	A	01-03-2001	AU 6895800 A	19-03-2001
			BR 0013439 A	30-04-2002
			EP 1210118 A2	05-06-2002
			NO 20020728 A	05-04-2002
			WO 0113904 A2	01-03-2001
DE 19927689	A	21-12-2000	DE 19927689 A1	21-12-2000
			AU 5680500 A	09-01-2001
			WO 0078294 A2	28-12-2000
			EP 1185253 A2	13-03-2002
DE 19940740	A	01-03-2001	DE 19940740 A1	01-03-2001
			AU 6279800 A	26-03-2001
			AU 6992100 A	26-03-2001
			AU 7511600 A	26-03-2001
			BR 0013825 A	23-07-2002
			BR 0013826 A	30-07-2002
			CZ 20020671 A3	12-06-2002
			CZ 20020673 A3	12-06-2002
			CZ 20020674 A3	15-05-2002
			WO 0115682 A1	08-03-2001
			WO 0115683 A1	08-03-2001
			WO 0115667 A1	08-03-2001
			EP 1207866 A1	29-05-2002
			EP 1207868 A1	29-05-2002
			EP 1207858 A1	29-05-2002
			NO 20020939 A	22-04-2002
			NO 20020974 A	27-02-2002
			NO 20020975 A	27-02-2002

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82